

PATENT
671308-2001.1**REMARKS**

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. Status Of Claims And Formal Matters

The specification has been amended to add a specific reference to prior applications and to delete an embedded hyperlink. No new matter has been added.

Claims 1-27 were under consideration in this application. Claims 1-3, 5, 8, 9, 15, 17, 18, 23, 26 and 27 have been canceled and claims 4, 10-14, 16, 21, 22, 24 and 25 have been amended. Support for the claim amendments is found throughout the specification as originally filed and in particular involve rewriting dependent claims as independent claims and correcting claim dependencies. No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Objection to the Specification Is Overcome

The disclosure was objected to for containing an embedded hyperlink and/or other form of browser-executable code. In response, the specification has been clarified to remove the hyperlink, thereby obviating the objection.

It is believed that the objection to the specification has been overcome. Reconsideration and withdrawal are respectfully requested.

3. The Claim Objections are Overcome

Claim 18 was objected to as allegedly being a substantial duplicate of claim 17. Claims 17 and 18 have been canceled, thereby rendering the objection moot.

Claim 22 was objected to because of a grammatical error in the format of the claim. Claim 22 has been amended in accordance with the Examiner's suggestion.

It is believed that the objections to the specification have been overcome. Reconsideration and withdrawal are respectfully requested.

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671308-2001.1**4. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome**

Claims 1-4, 6-12, 14-19, 21 and 24-25 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide enablement for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium selected from the group consisting of a genus *Bifidobacterium*. The Examiner states that the specification is enabling for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein.

Claims 1-3, 8, 9, 15, 17 and 18 have been cancelled, thereby obviating the rejection, in part.

Claims 4, 14, 16, 21, 25 has been clarified to recite a method encompassing pecifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein, thereby obviating the rejection.

Since claims 6, 7, 10-12 and 24 depend from claim 4, and claim 19 depends from claim 16, the rejection to claims 6, 7, 10-12, 19 and 24 have also been obviated.

It is believed that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome. Reconsideration and withdrawal are respectfully requested.

5. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 1-4, 6-20 and 24-25 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner alleges that claims 1-4, 6-15 and 24-25 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein.

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Claims 1-3, 8, 9, 15, 17 and 18 have been cancelled, thereby obviating the rejection, in part.

Claims 4, 14, 16 and 25 has been clarified to recite a method encompassing specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein, thereby obviating the rejection.

Since claims 6, 7, 10- 12 and 24 depend from claim 4, and claim 19 depends from claim 16, the rejection to claims 6, 7, 10-12, 19 and 24 have also been obviated.

It is believed that the rejections under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal are requested.

6. The Rejections Under 35 U.S.C. § 102 Are Overcome

Claims 1-3, 8, 9, 12, 14, 16, 19, 21 and 24 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Yazawa *et al.* (AJ, hereinafter "Yazawa"). Claims 1-4, 8, 9, 12, 14, 16-19, 21 and 24-25 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Babincova *et al.* (AW, hereinafter "Babincova"). Claims 16, 19 and 21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Matsumura *et al. et al.* (AM, hereinafter "Matsumura"). Claims 1-3, 8, 12, 14, 15, 16, 19, 21 and 24 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yazawa *et al.* (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999, hereinafter "Yazawa 2"). These rejections are respectfully traversed. These rejections are moot in light of the amendments to the claims submitted herein. The cited references do not anticipate the instant invention.

Claims 1-3 and 8 have been cancelled, thereby obviating the rejection, in part.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art

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reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention.

It is respectfully submitted that Yazawa is not prior art under the provisions of 35 U.S.C. §§ 102 or 103. Yazawa was published on March 27, 2000, while the filing date of the present application is March 26, 2001 with a priority date: September 21, 2000. Attached hereto is a Declaration Under 35 C.F.R. § 1.132 ("Declaration"). The Declaration is presently unsigned and a signed Declaration will be provided. Accordingly, Applicants submit that Yazawa is not prior art under 35 U.S.C. § 102(a).

Study (11) in Babincova is Yazawa. The description on *Bifidobacterium longum* in Babincova merely recites Yazawa (for example, see Babincova, page 2, 5th paragraph). As stated above, Yazawa is not prior art. Therefore, the description on *Bifidobacterium longum* in Babincova similarly cannot be a cited invention over the present invention. That is, the part of Babincova without the description of Study (11) should be regarded as a cited invention. In other words, Babincova relates to *Clostridium*, while does not disclose substantially *Bifidobacterium*. Accordingly, Babincova is different from the present invention and thus does not anticipate the present invention.

Matsumura relates to the construction of a shuttle vector pBLES100 by cloning a *Bifidobacterium longum* plasmid and a gene encoding spectinomycin adenylyltransferase AAD (9) from *Enterococcus faecalis* into the *Escherichia coli* vector pBR322.

Claims 16, 19, and 21 relate to pharmaceutical compositions comprising a transformed *Bifidobacterium*.. There is no description in Matsumura that the shuttle vector pBLES 100 can become a pharmaceutical composition having the characteristic of transporting the gene specifically to tumor tissues, of an individual with cancer patient under anaerobic condition.

Yazawa 2 pertains to the proliferation of *Bifidobacterium longum* specifically in tumor tissues and that *Bifidobacterium longum* can be used for cancer treatment as gene delivery vector. However, there are no specific descriptions on how *Bifidobacterium longum* is used, or on the genetic transformation system. Applicants respectfully remind the Examiner that a reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of

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the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985). Furthermore, claims 14, 16 and 21 have been amended, thus Yazawa 2 does not anticipate the presently claimed invention.

Consequently, reconsideration and withdrawal of the Section 102 rejections are earnestly requested.

7. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 1-4, 6-9, 17, 18 and 25 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa 2 taken with Brown (AC). Claims 1-3 and 6-7 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yazawa 2 taken with Brown (AC) and further in view of Blanche et al. (US 6,518,062). These rejections are respectfully traversed and are moot in light of the amendments to the claims submitted herein. The cited reference do not make the instant invention obvious.

Claims 1-3, 8, 9, 17 and 18 have been cancelled, thereby obviating the rejection, in part.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention.

As mentioned above, Yazawa 2 relates to the use of *Bifidobacterium longum* as a gene delivery vector to tumor tissue. However, there is no specific description on how to use *Bifidobacterium longum* or on the *Bifidobacterium longum* genetically modified.

Brown relates to a method for treating tumor tissues under anaerobic condition, by combining an enzyme (specifically nitroreductase) and a pro-drug, and to use a genetically modified bacterium (*Clostridium acetobutylicum*) to deliver an enzyme to the hypoxic/necrotic

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region of a tumor, and systemically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme. Moreover, the enzyme/pro-drug combination may be selected from nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs.

Considering the technical common knowledge at the time of filing that genetic characteristic of the genus *Bifidobacterium* was not known, as there was no reproducible system efficient for gene introduction and no sufficient selective marker, and that the development of controlling factor, such as a promoter to express protein encoded by the introduced gene in high concentration was not sufficient, a person of ordinary skill in the art could not prepare a genetically modified *Bifidobacterium longum*, in particular a *Bifidobacterium longum* wherein a controlling factor, such as a promoter to express protein encoded by the introduced gene (having an antitumor activity/having an activity of converting a precursor of an antitumor substance into the antitumor substance) in high concentration is added. Even by combining Yazawa 2 and Brown, a person of ordinary skill in the art could not easily presume the invention described in the presently claimed invention.

Blanche relates to enzyme combinations useful for destroying cells, particularly proliferative cells. Blanche also relates to vectors enabling the intracellular expression and transfer of the enzyme combinations, as well as their therapeutic use, particularly in anti-cancer gene therapy. Furthermore, Blanche pertains to introducing a vector having DNA encoding HSV1 thymidine kinase, and to administer ganciclovir to tumor tissues.

Blanche relates to a combination of enzyme and pro-drug, and HSV-1TK and ganciclovir, that is not described in Brown.

In view of the present claim amendments, there is no motivation to combine Yazawa 2, Brown and Blanche. Even if the references were combined, the combination of Yazawa 2, Brown and Blanche would not teach or suggest the presently claimed invention.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

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REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

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671308-2001.1**CONCLUSION**

In view of the remarks, amendments and Declaration, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: Deborah L. Lu
Thomas J. Kowalski
Reg. No. 32,147
Deborah L. Lu
Reg. No. 50,940
Telephone: (212) 588-0800
Facsimile: (212) 588-0500